

Peer Review File

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Reviewer A

The hypothesis of this study was that patients undergoing long-course palliative regimens spend a greater portion of their life receiving radiation treatments and higher rates of incomplete courses compared to those receiving single fraction treatments. In results, the percentage of remaining life spent receiving radiation therapy (PRLSRT) was significantly increased in those receive multifraction palliative regimens compared to single fraction RT. Authors suggested in conclusion that single fraction RT should be utilized to reduce time spent receiving treatment and the number of incomplete courses in the palliative treatment of painful bone metastases, particularly those with a poor prognosis such as metastatic HCC.

The prognosis of HCC is improved with the modern oncologic management and supportive care. The median survival of 3 months in this study was shorter than others of 5 to 11 months.(1-4) So, the patients in this study do not seem to represent the patients of HCC bone metastases. PRLSRT is sensitive to survival duration as well as RT period, and more prominent in the poor prognostic patients. In addition, there is not a cutoff or permissible level of PRLSRT for HCC bone metastases. Though the results are significant in this analysis, there may be limits to generalize them to the whole patients with HCC bone metastases.

RESPONSE: We agree that one must always use caution in generalizing data from any study or in comparing results between studies. In the four mentioned trials, the survival was calculated from the time of developing bone metastases, but in the present study the overall survival was calculated from start of radiation therapy. Patients may have asymptomatic bone metastases for some time before they progress to the point that they require radiation therapy for palliation. Additionally, the type of study and the data source will impact results. The present study is from sourced hospital registry data including information from hundreds of centers (both centers of excellence and centers lacking experience) and includes data where currents standards for metastatic HCC and bone metastases were followed, as well as, instances where they weren't. This data is a slice of what is actually happening across the board for this cancer. The suggested studies were small retrospective single institution reviews (n = 43 to 99) with exception of the Italian multi-institutional review (n=211). In these reports patients were treated much more uniformly (Bisphosphates, systemic therapy) compared to the presented report. The differences in treatments, patient characteristics, and in how OS was calculated does result in differences in the reported OS. With all this taken into consideration, we feel the presented results offers perspective of how HCC patients

with bone metastases requiring radiation fair and is unique in looking at the survival after RT, instead of after the development of bone metastases, which can be significantly different. We agree there is no generally accepted PRLSRT for HCC or any other malignancy, but many feel that a value of <10% (receiving palliative RT takes less than 10% of the remaining life) is a reasonable target.

1. Seo HJ, Kim GM, et al. ^{18}F -FDG PET/CT in hepatocellular carcinoma: detection of bone metastasis and prediction of prognosis. Nucl Med Commun. 2015 Mar;36(3):226-33. **RESPONSE:** This retrospective report of OS was only for 67 patients who had both PET and Bone scans to evaluate for bone metastases, so it was a very selective group. The median OS was 5 months, which was measured as the time from the diagnosis to bone metastases to the time of death/last follow-up. In the present study OS was calculated from the start of palliative RT treatment (as described in the Methods section). The time from the diagnosis of bone metastases to the start of RT will contribute to the reported differences in OS.
2. Honda Y, Aikata H, Honda F, et al. Clinical outcome and prognostic factors in hepatocellular carcinoma patients with bone metastases medicated with zoledronic acid. Hepatol Res. 2017 Sep;47(10):1053-1060. **RESPONSE:** This retrospective study of 99 patients shows OS of 11.5 months in a select group of patients with HCC bone mets treated with zoledronic acid. OS was calculated starting at the time of starting zoledronic acid. In this study radiation was typically used when there was severe pain associated with the bone metastases (~60% of patients). There was no information on the timing of radiation or survival afterwards so it is difficult to know how well this compares
3. Lu Y, Hu JG, Lin XJ, Li XG. Bone metastases from hepatocellular carcinoma: clinical features and prognostic factors. Hepatobiliary Pancreat Dis Int. 2017 Oct 15;16(5):499-505. **RESPONSE:** This small retrospective study included 43 patients from a single institution and reported a median survival of 11 month after the development of bone metastases. Like the other mentioned studies survival was measured from the time of the diagnosis of bone metastases not for palliative RT, which was received in 51%. This makes comparing survival difficult. Also in this study all patients received zoledronic acid and only 11.6% were metastatic to bone at presentation compared to 58% in the present study, which likely has prognostic implications.
4. Santini D, Pantano F, Riccardi F, et al. Natural history of malignant bone disease in hepatocellular carcinoma: final results of a multicenter bone metastasis survey. PLoS One. 2014 Aug 29;9(8):e105268. **RESPONSE:** This is a multicenter retrospective study of 211 patient with bone metastases from HCC. The majority of the patients were treated with Sorafenib (63%) and 50% received bisphosphonates. The median survival from time of bone metastases was 7 months, and less than 50% received RT to manage a skeletal-related event, which again makes it difficult to compare survival between this and the present study.

Changes to text: The 4 noted studies were included in the paper and the paragraph about limitation was revised to address the differences in OS, as well as, some of the generalizability of the present data.

” There were several limitations in this study. Like most large database retrospective studies, the population of patients who received 1fx was relatively low. Additionally, there was no data regarding pain response, quality of life information, retreatment, or the extent of systemic disease at time of RT treatment, which would have provided a more detailed analysis of response and outcomes. The PRLSRT metric is strongly influenced by short survival and radiation duration. Since patients in the present study had poor survival outcomes (median survival after radiation of about 3 months), some may question the generalizability of the study results and the PRLSRT metric, but this must be taken in context. It is acknowledged that several studies of HCC patients reported longer overall survival outcomes with median survival of 5-11 months (38-41), but these studies typically calculated survival from the diagnosis of bone metastases instead of the start of RT, included only 50-60% of patients who required palliative RT, and treated patients in more uniform manner with high proportions receiving systemic treatment with chemotherapy and bisphosphonates. Given these factors, the differences in the reported survival rates are not surprising since it could be months between the diagnosis of bone metastases and progression of the lesions to become symptomatic enough to require intervention with radiation. Additionally due to the rarity of the diagnosis, any center reporting significant numbers of patients with HCC bone metastases are likely centers of excellence with significant experiences managing metastatic HCC, especially compared to the patients in the current study, who were treated at every kind of center. Despite these limitations, the current study gives unique insight into the practice patterns and outcomes after palliative RT for BMs from HCC and is valuable because it is one of the only studies to report the survival from the time of radiation therapy, which is crucial for determining radiation fractionation. “

COMMENT: It is taken for granted that PRLSRT of single faction is less than that of multifractionated RT. Generally, we know that palliative effects were similar according to fractionation regimens of RT but re-irradiation rates are higher in shorter regimen compared to more protracted ones. Therefore, fractionation regimens of palliative RT should be decided with the consideration of the probability of re-irradiation, performance status, life expectancy, tumor volumes, status of primary HCC, etc.

RESPONSE: We agree that all those factors should be considered when choosing fractionation schedules. Unfortunately, the NCDB data did not include data regarding retreatment rates, but with the limited survival in many of these patients it is unlikely they lived long enough for retreatment to be required. For reference, in the Bone Pain Trial Working Group study the retreatment probability at 3 and 6 months was roughly 10% and 20% for single fraction and 5% and 10% for multi-fraction treatments. Steenland et al (Dutch Bone Met Trial) showed a median time to retreatment of 14 weeks for single fraction vs 23 weeks for multifraction regiments. Taken

together this data supports a relatively low need for retreatments in patients living only a few months.

Changes to Text: Some of the data in the response was added to the paragraph in the discussion discussing retreatment. Changes were made to highlight the low need for retreatments in patients with limited long-term survival.

Reviewer B

"Given the short survival time and the equivalence of single and multifraction regimens for the treatment of BMs, efforts should be made to reduce palliative RT duration to maximize patient quality of life."

This message is very important. However, this study has some serious limitations to solve for publication.

1. Although many patients treated with SRS were included, SRS may be inferior to conventional radiotherapy in terms of pain palliation based on RTOG0631 trial. If so, the rational that the author claims does not hold.

RESPONSE: In this trial the number of patients who received SRS was very low (<2% of population, but it was nearly 50% of the single fractions group, which was very small overall only 49 patients), as such we didn't discuss this and felt that it didn't contribute to the overall project. As the vast majority of the patients treated in this study received conventional radiation as opposed to SRS/SBRT, we don't think that the implications of RTOG 0631 (equivalent pain response at 3 months between single fraction SRS/SBRT and single fraction 8 Gy (Ryu ASTRO 2019)) impact our hypothesis, rational, or claims in any way.

Changes in Text: We clarified the number of patients who received SRS (n=24) in the results section to help people understand that the low percentage of people who receive SRS will not impact the study design, hypothesis, or results.

2. Authors evaluated the "percentage" of remaining life spent receiving radiation therapy (PRLSRT). However, is not it important for patients to have an "absolute" time without symptoms? I want to know authors' consideration about this.

RESPONSE: We agree the absolute time without symptoms is an important consideration for palliative RT. Unfortunately, the NCDB data doesn't include any data regarding symptoms, so this aspect of outcomes could not be addressed in this study. Given that the response to palliative radiation may take several weeks to reach full effect almost regardless of the fractionation scheme, for patients with poor prognosis and limited potential for long term survival, short courses should be used not only to achieve a meaningful pain response, but to do it in the manner that causes the least burden to the patient, thereby maximizing the palliative benefits.

Changes to text: No changes